PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SJB:TR:FP21104	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. **PCT**/AU2005/000141	International filing date *(day/month/year)* 3 February 2005	Priority date *(day/month/year)* 3 February 2004

International Patent Classification (IPC) or national classification and IPC

Int. Cl.

C12Q 1/68 (2006.01)

Applicant

HYBRID BIOSCIENCES PTY LTD et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
1 September 2005	05 June 2006
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **CHRIS LUTON** Telephone No. (02) 6283 2256

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2005/000141

Box No. I Basis of the report

1. With regard to the **language,** this report is based on:

[X] The international application in the language in which it was filed

[ ] A translation of the international application into , which is the language of a translation furnished for the purposes of:

[ ] international search (under Rules 12.3(a) and 23.1 (b))

[ ] publication of the international application (under Rule 12.4(a))

[ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

[ ] the international application as originally filed/furnished

[X] the description:

pages **1-68** as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[X] the claims:

pages **69-74** as originally filed/furnished
pages* **75-76** as amended (together with any statement) under Article 19
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[ ] the drawings:

pages as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages
[ ] the claims, Nos.
[ ] the drawings, sheets/figs
[ ] the sequence listing *(specify)*:
[ ] any table(s) related to the sequence listing *(specify)*:

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

[ ] the description, pages
[ ] the claims, Nos.
[ ] the drawings, sheets/figs
[ ] the sequence listing *(specify)*:
[ ] any table(s) related to the sequence listing *(specify)*:

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims **1-21, 27-29**	**YES**
	Claims **22-26**	**NO**
Inventive step (IS)	Claims **1-21, 27-29**	**YES**
	Claims **22-26**	**NO**
Industrial applicability (IA)	Claims **1-29**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1 – Mongelard et al.
D2 – Liu et al.
D3 – WO 2004/006678
D4 – WO 2003/016537
D5 – WO 2000/042838
D6 – Wu et al.
D7 – Zhang et al.
D8 – Romagnoli et al.
D9 – Trehan et al.
D10 – Steinmetz et al.
D11 – Cheng et al.
D12 – Borriss et al.
D13 – Scandalios et al.

The present invention relates to methods for identifying genes capable of contributing to hybrid vigour or hybrid debility. The present invention is based on the suggestion that hybrid mRNA molecules may be generated by a mechanism whereby sequences from alternative parental alleles are incorporated into the same mRNA transcript. The Applicant proposes that this occurs by the splicing of alternative exons from different alleles into the same transcript (page 3). This mechanism is proposed to result in a "hybrid mRNA". In the context of the present specification and claims, the phrase "hybrid mRNA" is construed as an mRNA molecule which includes exon sequences from alternative alleles.

NOVELTY (N) and INVENTIVE STEP (IS) Claims 22-26

None of D1-D13 disclose methods of identification of genes capable of producing hybrid vigour or debility comprising the steps of independent claims 1 or 14. Similarly, none of the documents disclose a method for producing hybrid vigour or debility having the steps of independent claim 21. None of the documents disclose the method of claim 27. Therefore, independent claims 1, 14, 21 and 27, and claims dependent therefrom, are novel in light of the cited prior art.

D1 describes a process whereby an mRNA is produced from sequences derived from separate alleles. D1 describes the process of "trans-splicing" and notes that such a process is capable of producing a normal transcript from two alternative non-functional alleles. The resulting "normal" transcript is a "hybrid mRNA" as defined by the present specification. D1 discloses methods whereby the sequences of hybrid transcripts are compared with those of the individual alleles. Thus, claim 22 is not novel and does not involve an inventive step in light of D1.

(continued on extra sheet ...)

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The specification generally describes a hypothesis for the known phenomenon of heterosis. The examples use the hypothesis to explain known, previously described phenomena. However, the specification wholly fails to demonstrate any of the methods or constructs of independent claims 21, 22, 23, 24 or 27.

The page numbering of the amendments made under Article 19 is inconsistent with the page numbering of the specification as filed. The Article 19 amendments are on page numbers 75 and 76 and include claims 22-29. However, original claims 22-29 are on pages 73 and 74 as originally filed. Moreover, the originally-filed abstract is on a page numbered 75.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

D1 discloses the production of constructs having the wild-type sequence for the mod(mdg4) gene. By comparison with the original mutated alleles, this construct represents a construct falling within the scope of claim 23. Thus, claim 23 is not novel and does not involve an inventive step in light of D1. The use of the construct to restore function in the mutant organism represents a method falling within the scope of claim 24. Thus, claim 24 and claims dependent therefrom are not novel and do not involve an inventive step in light of D1.

D2 and D3 disclose the use of trans-splicing to correct the sequence of mutant transcripts. D2 and D3 disclose the sequencing of corrected (hybrid) transcripts (and, inherently, a comparison against the sequences of the alleles). Therefore, claim 22 is not novel and does not involve an inventive step in light of D2 and D3. D2 and D3 disclose constructs for use in the described methods which fall within the scope of claim 23. Thus, claim 23 is not novel and does not involve an inventive step in light of D2 and D3. D2 and D3 disclose the use of such constructs to repair a defect (thus resulting in hybrid vigour). Such methods fall within the scope of claim 24. Thus, claim 24 and claims dependent therefrom are not novel and do not involve an inventive step in light of D2 and D3.

D4 describes methods for inducing trans-splicing of mRNAs to repair transcripts from mutant alleles and for the modification of transcripts generally. D4 describes the exchange of exons between RNA molecules (page 8, lines 5-7 & 15-20; page 9, lines 8-20). D4 also describes methods and kits for the identification of hybrid RNA molecules (page 53, line 17 to page 54, line 4; page 56, lines 32-34; page 75, lines 6-12; claim 44). The methods and kits disclosed by D4 fall within the scope of claims 23-26. Claims 23-26 are not novel and do not involve an inventive step in light of D4.

D1-D4 disclose the general concept that transcripts from alternative alleles may be recombined to form transcripts including sequences from alternative alleles. However, D1-D4 do not disclose or suggest that this mechanism may account for hybrid vigour. Therefore, independent claims 1, 14 and 21 and claims dependent therefrom involve an inventive step in light of D1-D4.

D5 describes methods of molecular profiling for heterosis. The methods of D5 rely on expression profiling including a comparison of expression levels between individual organisms and their parents. The methods of D5 do not involve an examination of mRNA transcripts for sequences derived from alternative alleles.

D6 also describes methods of molecular profiling for heterosis. The methods of D6 rely on expression profiling including a comparison of expression levels between individual organisms and their parents. The methods of D6 do not involve an examination of mRNA transcripts for sequences derived from alternative alleles. D6 discloses the presence of transcripts in hybrid plants but not in the parents (p285, 1st column). D6 discloses that many of the transcripts showed no homology to any known gene (p283, 1st column). However, D6 does not disclose or suggest a comparison of the sequence of a transcript against the individual allelic sequences.

D7 describes methods of molecular profiling for heterosis that rely on examining patterns of differential gene expression between hybrids and their parents. D7 does not disclose or suggest a comparison of the sequence of a transcript against the individual allelic sequences.

D8 describes methods of molecular profiling for heterosis based on differential expression analysis. D8 does not disclose or suggest a comparison of the sequence of a transcript against the individual allelic sequences.

D9 examines heterodimeric enzymes as a molecular basis for heterosis. D9 does not disclose or suggest that transcripts may include sequences derived from alternative alleles.

D10 discusses the contribution that different alleles make to a certain phenotype (Htg+) but does not investigate whether sequences from alternative alleles are combined in mRNA transcripts.

(continued ...)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

D11 examines differential display of mRNA between hybrids and parental lines in maize. D11 does not disclose or suggest a comparison of individual mRNA transcript sequences against the allelic sequences.

D12 examines hybrid bacterial enzymes. D12 does not disclose or suggest a comparison of individual eukaryotic mRNA transcript sequences against the allelic sequences.

D13 examines hybrid enzymes formed as heteromultimers as a molecular basis for heterosis. D13 does not disclose or suggest a comparison of individual eukaryotic mRNA transcript sequences against the allelic sequences.